ORIGINAL ARTICLE

Impact of TB on the survival of people living with HIV infection in England, Wales and Northern Ireland

Dominik Zenner,[1,2] Ibrahim Abubakar,[1,2] Stefano Conti,[1] Rishi K Gupta,[3] Zheng Yin,[1] Meaghan Kall,[1] Michelle Kruijshaar,[4] Brian Rice,[1] H Lucy Thomas,[1] Anton Pozniak,[5] Marc Lipman,[3] Valerie Delpech[1]

ABSTRACT

Introduction The impact of TB disease on survival in people living with HIV in high resource settings is not well documented in the antiretroviral treatment (ART) era. We calculated TB incidence rates and compared the mortality of persons with and without HIV-TB in a UK HIV cohort in the post-ART era, to determine the impact of HIV-TB on survival in the UK.

Methods We linked the national cohort of persons (aged ≥15 years) diagnosed with HIV between 2000 and 2008 in England, Wales and Northern Ireland with the national TB register and deaths from the Office of National Statistics. We compared all-cause and AIDS-specific mortality in patients with and without TB by estimating HRs using Cox regression modelling allowing for potential predictors.

Results Overall, 3188 (7.2%) individuals developed TB infection among a cohort of 44 050 HIV-diagnosed persons and 149 663 person-years. The cumulative TB incidence rate was 2.13 per 100 person-years with a spike within the first 6 months after HIV diagnosis. TB coinfected patients comprised 18% of the 1880 deaths during follow-up and 79% of deaths (n=967) in the year following HIV diagnosis. TB coinfection (HR 4.77, 95% CI 4.11 to 5.54) was significantly associated with increased all-cause mortality. Analysis of AIDS-related survival showed similar results.

Discussion The unexpected high mortality in patients with HIV-TB in a population with good healthcare access and ART availability highlights the importance of improving active and latent TB case-finding among patients with HIV, and HIV-testing among patients with TB, to ensure appropriate and prompt treatment initiation for both diseases.

Key messages

What is the key question?
► What is the TB incidence and the impact of TB coinfection on survival of people living with HIV (PLHIV) in the era of antiretroviral treatment (ART) in the UK?

What is the bottom line?
► PLHIV continue to have high rates of TB coinfection, which are associated with unexpectedly high mortality rates, even after adjusting for confounders including CD4 count and ART.

Why read on?
► This study of a large national HIV cohort demonstrates the impact of late diagnosis and delayed treatment on mortality in the UK and highlights the need for active and latent TB case finding among people with HIV and also the need to offer and recommend HIV testing to patients with TB.

INTRODUCTION

The global burden of TB and HIV coinfection remains considerable, with an estimated 1.1 million new cases in 2011 alone.[1] The use of highly effective antiretroviral therapy (ART) has greatly improved survival in HIV-infected individuals, including those with TB.[2] Despite this, over 430 000 people coinfected with TB and HIV died globally in 2011 representing almost a third of all TB deaths[1] and a quarter of HIV-related deaths.[2]

In the UK, the incidence of TB among adults living with diagnosed HIV fell from 3020 per 100 000 in 2002 to 400 per 100 000 in 2011.[3] This prominent decline coincided with a reduction in new HIV diagnoses among migrants from sub-Saharan Africa (SSA), the group most likely to have been exposed to TB.[3] In addition, there was a large year on year increase in the total number of people living with diagnosed HIV infection as a result of improved survival and new HIV diagnoses leading to a larger cohort. In contrast, over the same time period the overall incidence of TB in the general population has risen, and, although a low incidence country by WHO standards, the UK now has the second highest TB incidence rate in Western Europe, at around 14 per 100 000.[4] Approximately 4% of adult TB cases had underlying HIV infection in 2011.[5]

HIV-TB survival is setting specific[2] and among other things, is determined by the number of patients with undiagnosed HIV, the availability of ART and the ability to detect and treat TB promptly. European cohorts have documented lower survival rates of coinfected patients in the

East compared with the West, associated with poor access to ART.[6] [7] Improved outcomes through prompt initiation of ART and TB treatment are well documented in HIV and TB endemic areas.[8] [9] However, observed outcomes from studies set in countries with poor health infrastructure may not be readily transferable to a resource-rich setting.

A recent meta-analysis of cohort studies assessing the effect of TB on mortality in persons with HIV infection found that TB was associated with an overall twofold increase in mortality.[10] However, when restricted to a subset of six studies conducted in the ART era, TB coinfection no longer had a significant impact on survival. None of the ART-era studies were conducted in an industrialised country, and authors recommended that further studies are needed to be conducted in different settings, with the inclusion of documentation of exposure and adherence to ART.

While life expectancy in people treated for HIV infection in the UK has dramatically increased with the advent of ART, it remained about 13 years less than that of the general population in 2008.[11] Treatment delay due to late HIV presentation is the most important predictor of short-term[12] and long-term survival.[11] Although TB cases continue to account for 15% of all reported AIDS cases,[3] [13] there is currently little understanding of the impact of TB on the survival of persons living with HIV infection. Small-scale studies have shown a decline in TB-HIV mortality following the advent of universally available ART[14] and demonstrated the benefits of simultaneous TB and HIV treatment.[15]

The UK has well-established diagnostic facilities for TB and HIV infection and universal availability of ART and anti-TB treatment. In addition, comprehensive surveillance and monitoring data collected through the National Health Service provide a unique opportunity to evaluate the impact of clinical and public health policies. In this study, we use comprehensive data from the national HIV cohort linked to national TB surveillance data and deaths from vital statistics to present TB incidence density rates from the time of HIV diagnosis and assess the impact of TB coinfection on the survival of HIV-diagnosed persons. In contrast to most clinical cohorts, persons are enrolled in this national HIV cohort at the time of HIV diagnosis (allowing capture of the two-thirds of TB and HIV coinfections diagnosed simultaneously). Furthermore, the annual loss to follow-up in this national HIV cohort is very low (<5%) due to comprehensive data returns (including transfers) from all HIV services across the UK linked to service funding.[16]

The main objectives of the study were to compare the survival of HIV-diagnosed patients with and without TB coinfection and assess the impact of TB coinfection on survival after adjusting for potential explanatory variables. The large cohort and detailed clinical history allows an evaluation of the impact of TB infection by site of disease. In addition to providing an evidence base on the continued impact of TB coinfection in high resource settings in the ART era, the study provides an assessment of current public health policies with regard to testing, treatment and prevention of HIV and TB infections.

METHODS
Data sources
Data from the national HIV cohort were linked to the national enhanced TB surveillance system (ETS) and the death register of the Office for National Statistics. HIV and TB databases are held securely at Public Health England and comply with the data protection legislation.[5] [16] Clinic, laboratory and death records within and across years are routinely linked to form a national

HIV cohort. No names are collected on HIV databases at Public Health England. Linking is conducted using a coding system of the surname, gender and date of birth. This cohort includes comprehensive demographic and exposure category information on all adults (aged ≥15 years) diagnosed with HIV infection and prospective clinical information obtained at least annually from all HIV clinics as well as ART usage and all sequential CD4 counts reported directly by laboratories.

TB cases among the HIV cohort were identified using probabilistic record linkage with ETS consisting of demographic and microbiological information and clinical outcomes. Matches were based on the agreement, partial agreement or disagreement between data fields in pairs of records based on initial work by Newcombe[17] and tailored to the use of infectious disease surveillance data.[18]

Study population and observation time
We carried out a retrospective cohort study and included all persons aged ≥15 years, diagnosed with HIV infection in England, Wales and Northern Ireland (EWNI) between 2000 and 2008. Patients entered the cohort upon first recorded HIV diagnosis or tests indicating the diagnosis (eg, first CD4 count) and exited at date last seen for HIV care prior 2008 or date of death (if applicable). All remaining observations were censored at the end of 2008. Deaths occurring between 2000 and 2008 were analysed as recorded by 31 December 2010 (box 1).

Data analysis
After cleaning and deduplication of the merged databases, we described the clinical and demographic characteristics of the HIV cohort with and without TB coinfection. Descriptive analysis included cross-tabulations and calculation of mean values and medians as appropriate. Significance tests were performed with t tests for parametric and Wilcoxon rank-sum tests for nonparametric data. Proportions were compared with χ^2 tests.

We analysed survival using a multivariable time-to-event analysis. After checking the validity of the proportional hazards assumption in our data using Schoenfeld's residuals,[19] we modelled all cause and AIDS-specific time to death with a Cox proportional hazards model. We included variables in a stepwise fashion using Akaike Information Criterion[20] to decide on the additional explanatory power of each candidate predictor while controlling for model parsimony. For AIDS-specific

---

Box 1 Definitions

▶ *TB disease* was defined as having evidence of a positive culture of *Mycobacterium TB* complex or, in the absence of culture confirmation, clinical and/or radiological evidence of TB with report of a full course of anti-TB treatment. Pulmonary and extrapulmonary TB events were both considered. TB events could precede the first HIV diagnosis by 1 year, as late HIV diagnosis is a likely occurrence in this population group.[16] Earlier TB events were excluded from analysis.

▶ *Late HIV diagnosis* was defined as an HIV diagnosis with a CD4 count <350 cells/μL reported within 91 days of diagnosis.

▶ *Simultaneous HIV/TB coinfection* was defined as occurrence of these diagnoses within 91 days of each other.[16]

survival analysis, non-AIDS deaths were modelled alongside AIDS-related deaths within a 'competing risks' framework.

Variables showing a statistically significant effect and where effect modification was clinically plausible were tested for interactions. We took the magnitude of HRs and the width of their CIs into account to decide whether associations were clinically as well as statistically significant. Data analysis was carried out using STATA V.12 (Stata Corporation, College Station, Texas, USA) and MS Excel 2010 (Microsoft Corporation, Redmond, Washington, USA) for figures.

RESULTS
Baseline characteristics

Table 1 shows the baseline characteristics of the cohort, stratified by TB-HIV coinfection. The cohort consisted of all 44 050 persons diagnosed with HIV and seen for care in EWNI

Table 1 Baseline characteristics of a national HIV cohort diagnosed between 2000 and 2008 in England, Wales and Northern Ireland, stratified by TB coinfection

	Not coinfected		TB-HIV coinfected		Total	
	Number	Per cent	Number	Per cent	Number	Per cent
Total cases	40 862	92.8	3188	7.2	44 050	100.0
Cohort years	137 826.4		11 836.8		149 663.2	
Age and sex						
Median age (IQR) at HIV diagnosis	34.4	28.8–41.0	34.9	29.9–40.4	34.5	28.8–41.0
Male sex	25 217	61.7	1470	46.1	26 687	60.6
Ethnicity						
White	17 976	44.0	299	9.4	18 275	41.5
Black-African	17 230	42.2	2499	78.4	19 729	44.8
Black Caribbean and Black-Other	2285	5.6	108	3.4	2393	5.4
South Asian	472	1.2	76	2.4	548	1.2
Other Asian/Oriental	660	1.6	78	2.4	738	1.7
Other/mixed	1576	3.9	87	2.7	1663	3.8
World region of birth						
UK	11 568	28.3	192	6.0	11 760	26.7
Africa	15 670	38.3	2317	72.7	17 987	40.8
Asia	883	2.2	135	4.2	1018	2.3
Australasia	258	0.6	1	0.0	259	0.6
Europe	2385	5.8	75	2.4	2460	5.6
Latin America (incl. Caribbean)	1428	3.5	35	1.1	1463	3.3
North America	278	0.7	4	0.1	282	0.6
Abroad not specified	198	0.5	10	0.3	208	0.5
Not known	8194	20.1	419	13.1	8613	19.6
Probable route of transmission						
Sex between men	15 037	36.8	198	6.2	15 235	34.6
Injecting drug use	676	1.7	58	1.8	734	1.7
Heterosexual sex	23 667	57.9	2839	89.1	26 506	60.2
Blood/blood products	124	0.3	12	0.4	136	0.3
Mother-to-child trans	20	0.0	2	0.1	22	0.0
Other/Not known	1338	3.3	79	2.5	1417	3.2
CD4 categories						
≥500	10 329	25.3	214	6.7	10 543	23.9
350–499	8191	20.0	309	9.7	8500	19.3
200–349	9611	23.5	603	18.9	10 214	23.2
100–199	5462	13.4	727	22.8	6189	14.0
50–99	2696	6.6	488	15.3	3184	7.2
<50	4573	11.2	847	26.6	5420	12.3
Start of ART after HIV diagnosis						
ART start <91 days	12 415	30.4	1331	41.8	13 746	31.2
ART start 91–365 days	6525	16.0	760	23.8	7285	16.5
ART start >365 days	10 561	25.8	655	20.5	11 216	25.5
Never on ART	10 926	26.7	409	12.8	11 335	25.7
ART interruption	3229	10.9	259	9.4	3488	10.8
TB site of disease						
Pulmonary TB	n/a	n/a	1821	57.1	1821	4.1
ExtrapulmonaryTB	n/a	n/a	945	29.6	945	2.1
Miliary TB or TB meningitis	n/a	n/a	333	10.4	333	0.8

Numbers and proportions are given, except where denoted.
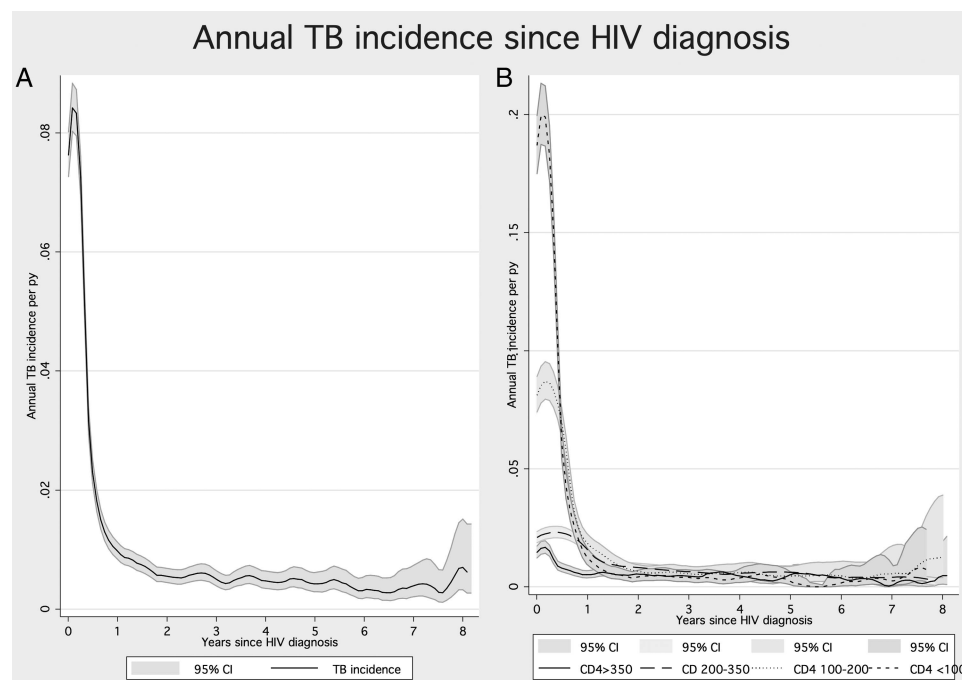ART, antiretroviral combination therapy.

Figure 1 Annual TB incidence density rates among a national HIV cohort (n=44 050) diagnosed between 2000 and 2008 in England, Wales and Northern Ireland by time since HIV diagnosis (A) and stratified by CD4 count at HIV diagnosis (B).

between 2000 and 2008 with a total follow-up time of 149 663 years and a median follow-up time of 3.1 years. Sixty-one per cent were men and the median age at HIV diagnosis was 34.5 years. The majority of persons were born in SSA (40.8%) or the UK (26.7%), and of Black African (44.8%) or white ethnicity (41.5%). More than half (56.8%) were late HIV presenters (table 1).

TB coinfection and incidence density rates

A total of 3188 (7.2%) persons in the cohort developed TB coinfection during follow-up. Compared with those without TB, the coinfected cohort comprised a higher proportion of women (p<0.001), black Africans born in SSA (p<0.001) and persons reporting heterosexually acquired HIV transmission (p<0.001). Most patients with TB were diagnosed with HIV late (CD4 count <350 cells/μL; 83.6%) and consequently ART uptake was high (87.2%). The median time between TB and HIV diagnosis was short (35 days, IQR 6–192 days). The most common TB disease was pulmonary TB (PTB, 58.8%) followed by extra-PTB (ETB, 30.5%) and miliary or central nervous system TB (10.8%; table 1).

The overall cumulative TB incidence rate of the HIV cohort was 2.13 per 100 person-years (py). The largest TB incidence density rates were observed within 6 months after HIV diagnosis (9.21 per 100 py) and dramatically decreased thereafter (0.72 and 0.32 per 100 py at 1 and 8 years post HIV diagnosis; figure 1A). Early TB incidence was dramatically affected by CD4 count at diagnosis (figure 1B). The incidence density rate at 6 months in those with a CD4 count <100 was 26.6 versus 1.9 per 100 py among those with a CD4 >350. TB incidence within 1 year of HIV diagnosis did not show a clear trend during our follow-up time and remained similar (6.92 per 100 py in 2008).

Descriptive analysis of deaths

A total of 1880 (4.3%) persons died from any cause during follow-up, of whom 898 (47.8%) were AIDS related. An

AIDS-defining *illness* prior to or at the time of death was reported for 1162 (61.8%) deaths including 341 persons with TB coinfection (representing 29.3% of AIDS deaths and 18.1% of all deaths). Almost two-thirds (64.5% (220/341)) of deaths among TB coinfected patients occurred within 3 months of simultaneous TB and HIV diagnosis. The median time between HIV diagnosis and death was significantly shorter for coinfection patients compared with those without TB (305 vs 508 days, p=0.002).

Survival

Survival was plotted via Kaplan–Meier curves (figure 2A, B), stratified by CD4 categories at HIV diagnosis and TB infection. Figure 2A, B shows that overall and in each CD4 category, the survival probability of TB coinfected patients was lower than in those without TB. Lower survival was particularly marked among patients diagnosed with CD4 count of <200 cells/μL. The 1-year probability of survival after HIV diagnosis for TB coinfected patients was 93.2% (95% CI 92% to 94%) compared with 98% (95% CI 97.8% to 98.1%) for those without (p<0.001; table 2). Between 2000 and 2007, 1-year survival improved overall (from 96.5%; 95% CI 95.7% to 97.2% to 98%, 95% CI 97.5% to 98.3%, p<0.001), but not for those with TB coinfection (92.1%, 95% CI 87.5% to 95.1% to 93.2% 95% CI 89.4% to 95.7%).

In the multivariable Cox proportional hazard model, those with TB coinfection had a 4.8 times higher hazard of death (95% CI 4.11 to 5.54) compared with those without TB. After stratifying by site of disease, those with miliary TB or TB meningitis had the highest risk (HR 6.96, 95% CI 5.10 to 9.51), followed by ETB (HR 4.92, 95% CI 3.92 to 6.17) and PTB (HR 4.32, 95% CI 3.60 to 5.17). Due to low numbers (n=27), it was not possible to include multidrug-resistant tuberculosis (MDR-TB) in the regression model. Other variables significantly associated with worse survival in the multivariable analysis included CD4 <350 at diagnosis, AIDS-defining illnesses other
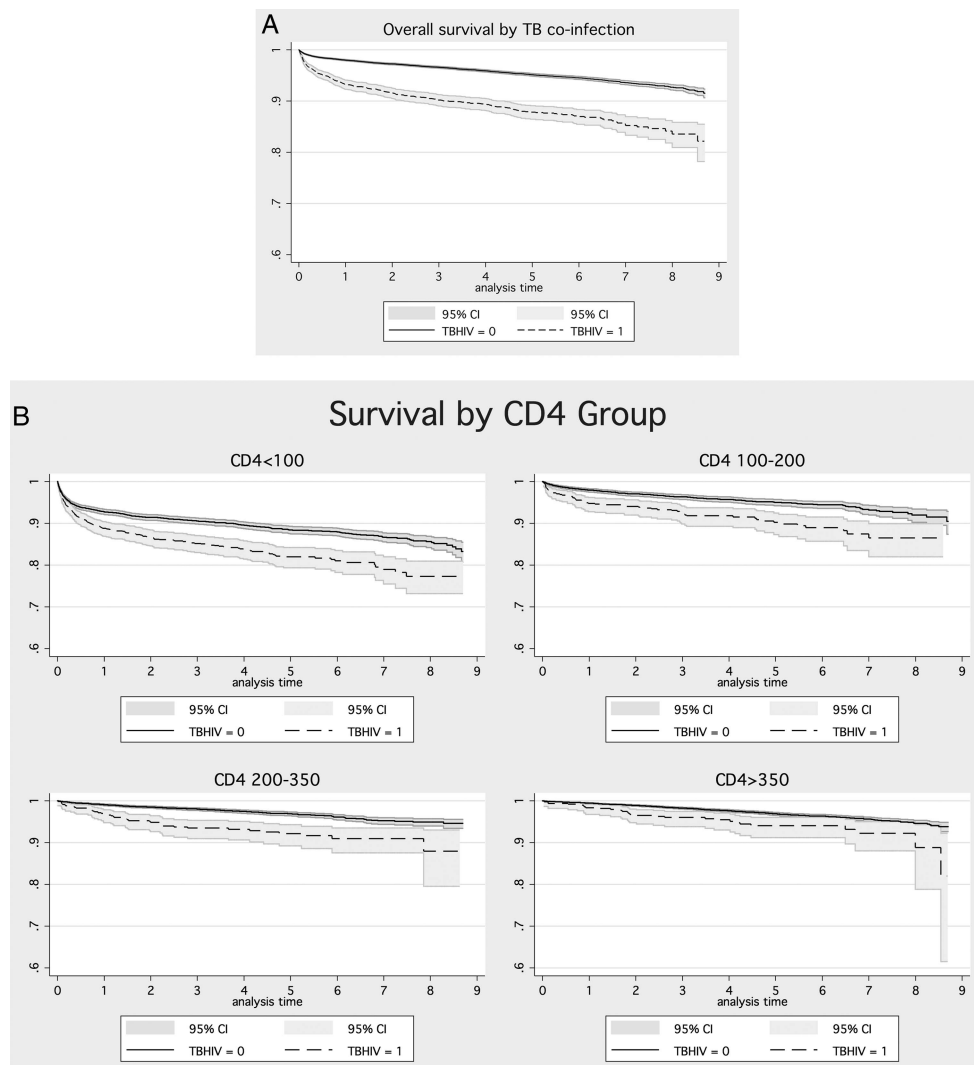
Figure 2 All-cause survival in a national HIV cohort (n=44 050) diagnosed between 2000 and 2008 in England, Wales and Northern Ireland stratified by TB-HIV coinfection status (A) and by CD4 count at diagnosis (B).

than TB, never having received ART or late ART start, older age at HIV diagnosis, male sex and injecting drug use or heterosexual sex as probable route of HIV exposure (table 3).

The Cox regression modelling approach was also adopted for AIDS-specific survival and shows very similar results, although with slightly different effect estimates (see online supplementary appendix table). We tested for, but did not find significant evidence of effect modification between exposure variables in both analyses.

DISCUSSION
We provide national incidence and survival analyses among persons living with HIV and TB coinfection in a high resource country with free and accessible HIV and TB treatment and care. Our findings show that between 2000 and 2008 the incidence of TB among HIV-diagnosed persons remained very high in the first 6 months after HIV diagnoses. After adjusting for a range of factors expected to affect survival, including low CD4 count at diagnosis, the risk of death in TB coinfected patients was almost five times higher than in those without TB coinfection.

The 1-year survival after HIV diagnosis was significantly worse for people with HIV-TB coinfection compared with those without (93% vs 98%). In keeping with improved survival

among people diagnosed with HIV in the UK,[21] we observed an increase in the 1-year survival after HIV diagnosis over the observational period. However, there was no similar trend observed among those coinfected with TB. Overall, nearly one-fifth of all deaths in people living with HIV occurred in those with TB, demonstrating the considerable population-level burden imposed by TB.

The magnitude of the impact of TB on survival identified in our cohort was unexpected. A recent meta-analysis of HIV cohort studies primarily observed in SSA found nearly a twofold increase in mortality among TB coinfected persons. However, the small subset of studies conducted in the ART era in high resource settings reported no evidence of increased mortality.[10] Importantly, most (80%) of the TB coinfected patients in our cohort were born in SSA and were likely to have acquired both infections in their country of origin. The similarities of key clinical features of our TB coinfected cohort with what may be expected in high burden countries—a very low CD4 count at diagnosis, a late or non-start of ART and subsequent ART treatment interruptions[7 10]—may be one explanation for the higher mortality observed in our cohort.

Most deaths in our cohort occurred within the first year (table 2), similar to previous studies.[22] A large proportion of

Table 2 Survival probabilities of a national cohort diagnosed between 2000 and 2008 in England, Wales and Northern Ireland by year since HIV diagnosis and TB coinfection

Cohort time (years)	Number at risk	Deaths	Survival Fn	95% CI
Patients without TB coinfection				
1	31 709	762	0.980	0.978 to 0.981
2	25 846	220	0.972	0.971 to 0.974
3	20 702	159	0.966	0.964 to 0.968
4	15 602	130	0.959	0.957 to 0.961
5	11 134	108	0.951	0.949 to 0.954
6	7293	60	0.945	0.942 to 0.948
7	4234	55	0.936	0.932 to 0.940
8	1771	27	0.927	0.922 to 0.932
TB coinfected patients				
1	2578	205	0.932	0.923 to 0.941
2	2216	43	0.916	0.905 to 0.925
3	1840	31	0.902	0.890 to 0.912
4	1451	15	0.894	0.881 to 0.905
5	1047	22	0.878	0.864 to 0.891
6	655	8	0.870	0.855 to 0.883
7	360	9	0.852	0.833 to 0.869
8	144	4	0.836	0.809 to 0.859

Estimates after year 8 are unstable as based on small numbers and therefore omitted here.
Fn, function.

individuals with low initial CD4 count and/or TB coinfection in the cohort had a late ART initiation. Although delays between HIV diagnosis and ART initiation reduced over the observation period (196–164 days for those with CD4 <350), some delays persisted throughout the entire cohort time and featured as an independent risk factor for poor survival after adjusting for late diagnosis. Historically, delays in ART initiation until 2 months into TB treatment used to be common for fear of toxicity, pill burden and convalescent immunological changes.[23] The importance of early ART initiation among TB coinfected patients has been demonstrated in the UK[15] and elsewhere.[10][24] Current guidelines recommend starting ART as soon as practicable in TB coinfected individuals, particularly in those with advanced immunodeficiency.[25] The observed increased short-term and long-term mortality among patients with late or non-start of ART and low CD4 count in our study supports current recommendations.[25]

The analyses of this paper are based on the very complete national TB surveillance system linked to a large and comprehensive national HIV cohort from the time of diagnosis and up to 9 years of follow-up, with few losses to follow-up. Linking provided the unique opportunity to include TB disease at the time of, and prior to, HIV diagnosis. We observed that the majority of HIV and TB diagnoses were made simultaneously, resulting in a prominent peak in TB incidence within the first few months of HIV diagnosis. Consequently, we show TB incidence rates among HIV diagnosed to be much higher than observed in clinical HIV cohorts both in the UK[26] and in other European cohorts.[27]

In the UK, diagnosed persons with HIV infection who are promptly linked to and retained in care[28] and those diagnosed at CD4 >350 can expect a near normal life expectancy.[11] The decreased survival found in our study is largely the result of late HIV diagnosis and delayed start of treatment. This represents considerable missed opportunity for early HIV diagnosis and treatment, particularly among persons from SSA. It highlights the importance of early HIV testing in primary and secondary care settings in high-prevalence areas as recommended by national guidance.[25]

Our study also emphasises the need for TB prevention activities among patients living with diagnosed HIV infection. There is evidence that treatment for latent TB infection (LTBI) in HIV-positive individuals is effective in preventing TB disease.[29][30] Intensified LTBI screening and treatment among migrants from high TB incidence countries and those with low CD4 count are recommended in the UK.[24][25] Strengthening its implementation may help preventing TB coinfection in the almost 40% who did not have a simultaneous diagnosis.

This study has a number of limitations. The cohort comprises persons living with diagnosed HIV, and persons presenting with TB disease not tested for HIV infection will have been missed. Although HIV screening is recommended for all patients diagnosed with TB, implementation of this policy is variable across TB clinics. It is likely that TB patients with undiagnosed HIV would have worse outcomes. Underdiagnosis of HIV infection in TB patients may have therefore lead to an overestimate of observed survival rates among coinfected patients. Results of the multivariate analyses rely on the availability of information collected through routine surveillance; although completion rates are generally high, these may be subject to small misclassification errors. Factors such as other comorbidities are not routinely collected in either surveillance system and are therefore not included in the model. Furthermore, some variables (eg, ART start variable) and late survival estimates could be influenced by a degree of survivor bias, which would underestimate late mortality or TB incidence by excluding early deaths from calculations. Finally, while deaths and death dates are recorded with near-complete accuracy in the UK through linking with the Office of National Statistics, there is a potential for misclassification of the cause of death.

In conclusion, the results of this large national cohort study demonstrate high rates of TB coinfection and subsequent mortality in people living with HIV, even after adjusting for confounders including CD4 count and ART treatment. As the burden of unrecognised HIV and TB infection in the UK remains high, there is a need to improve efforts for early detection and intervention for both HIV and TB. Our findings support recommendations for LTBI screening among HIV infected individuals from TB high incidence areas and

Table 3 Results of the single and multivariable Cox regression analysis of all-cause mortality in the national HIV cohort (n=44 050) 2000–2008, England, Wales and Northern Ireland

Characteristic	Number	HR (unadjusted)	95% CI	Hazard ratio (adjusted)	95% CI	p Value
TB-HIV						
Yes	3188	2.663	2.368 to 2.995	4.774	4.114 to 5.540	<0.001
No	40 862	1.000				
Site of TB disease						
Pulmonary TB	1821	2.440	2.091 to 2.847	4.316	3.604 to 5.169	<0.001
Extrapulmonary TB	945	2.606	2.129 to 3.19	4.918	3.922 to 6.168	<0.001
Miliary TB or TB meningitis	333	4.113	3.103 to 5.451	6.961	5.096 to 9.509	<0.001
No TB	40 862	1.000				
Earliest CD4						
CD4 <100	8604	4.939	4.398 to 5.547	3.532	2.983 to 4.182	<0.001
CD4 100–199	6189	2.032	1.747 to 2.364	2.789	2.317 to 3.356	<0.001
CD4 200–349	10 214	1.180	1.011 to 1.377	1.822	1.538 to 2.159	<0.001
CD4 >350	19 043	1.000				
AIDS (excl. TB)						
Yes	3625	8.490	7.748 to 9.302	7.380	6.456 to 8.436	<0.001
No	40 425	1.000				
Age at HIV diagnosis (years)						
15–24	4937	0.720	0.579 to 0.894	0.887	0.706 to 1.115	0.3
25–34	18 190	1.000				
35–44	14 102	1.713	1.527 to 1.921	1.586	1.404 to 1.792	<0.001
45–54	4903	2.736	2.389 to 3.133	2.215	1.911 to 2.568	<0.001
>55	1918	5.215	4.478 to 6.073	3.580	3.021 to 4.242	<0.001
Sex						
Female	17 363	0.672	0.609 to 0.742	0.745	0.659 to 0.841	<0.001
Male	26 687	1.000				
Start of ART (if CD4<350)						
Never on ART	2836	5.850	5.134 to 6.666	5.875	4.759 to 7.252	<0.001
ART start >365 days	4712	0.532	0.442 to 0.639	1.328	1.133 to 1.558	<0.001
ART start 91–365 days	5483	1.150	1.000 to 1.322	1.618	1.410 to 1.857	<0.001
ART start <91 days	11 693	1.000				
ART interruption (if ever on ART)						
No	28 759	0.996	0.842 to 1.177	0.598	0.503 to 0.712	<0.001
Yes	3488	1.000				
Probable route of exposure						
Injecting drug use	734	3.794	3.034 to 4.744	3.701	2.907 to 4.713	<0.001
Heterosexual sex	26 506	1.160	1.048 to 1.285	1.212	1.052 to 1.396	0.008
Blood/blood products recipient	136	1.320	0.626	2.782		
Mother-to-child transmission	22	1.673	0.235	11.898		
MSM	15 235	1.000				
Region of birth						
Western non-UK	2742	0.650	0.527 to 0.800	0.727	0.586 to 0.901	0.004
SSA	17 987	0.696	0.630 to 0.769	0.808	0.702 to 0.930	0.003
Other	2948	0.648	0.532 to 0.789	0.707	0.574 to 0.870	0.001
UK	11 760	1.000				
Ethnicity						
Black-Caribbean	1510	0.860	0.663	1.114		
Black-African	19 729	0.828	0.751	0.913		
Black-Other/Black-Unspecified	883	0.634	0.426	0.943		
Indian/Pakistani/Bangladeshi	548	0.909	0.601	1.375		
Other/mixed	1663	0.581	0.429	0.786		
Other Asian/Oriental	738	0.722	0.481	1.083		
Not known	704	2.984	2.318	3.840		
White	18 275	1.000				
MDR-TB						
Yes	27	3.330	1.470	7.544		
No	1685	1.000				

Continued

Table 3 Continued

Characteristic	Number	HR (unadjusted)	95% CI	Hazard ratio (adjusted)	95% CI	p Value
INH-resistant TB						
Yes	128	1.599	0.992 to 2.577			
No	1757	1.000				
Year of HIV diagnosis						
2000	2729	1.000				
2001	3673	0.872	0.718 to 1.058			
2002	4432	0.971	0.803 to 1.174			
2003	5341	0.839	0.690 tot 1.019			
2004	5828	0.896	0.737 to 1.090			
2005	5996	0.907	0.741 to 1.111			
2006	5429	0.901	0.725 to 1.120			

The baseline patient is characterised as a UK-born MSM aged 25–34 years who had a timely start on ART, ART interruptions, is not TB coinfected and has a CD4 count of $\geq$350 cells/µL at diagnosis.
ART, antiretroviral combination therapy; MSM, men who have sex with men; SSA, sub-Saharan Africa; MDR-TB, multidrug-resistant tuberculosis; INH, isoniazid.

increased HIV testing in a wide range of primary and secondary care settings.

Author affiliations
[1]Respiratory Diseases Department, Centre for Infectious Disease Surveillance and Control, Public Health England, London, UK
[2]Research Department of Infection and Population Health, University College London, London, UK
[3]Division of Medicine, University College London, London, UK
[4]Erasmus MC University Medical Center, Sophia Children's Hospital, Rotterdam, Netherlands
[5]Chelsea & Westminster Hospitals NHS Foundation Trust, London, UK

REFERENCES
1 World Health Organisation. *Global Tuberculosis Report 2012*. 2012. http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf
2 Joint United Nations Programme on HIV/AIDS (UNAIDS). *UNAIDS report on the Global AIDS Epidemic, 2012*. 2012. http://www.unaids.org/globalreport/global_report.htm
3 Public Health England. *HIV in the United Kingdom 2013 report*. 2013. http://www.hpa.org.uk/Publications/InfectiousDiseases/HIVAndSTIs/1311HIVintheUk2013report/
4 European Centre for Disease Prevention and Control. Tuberculosis surveillance and monitoring in Europe 2014. 2014. http://www.ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1050
5 Public Health England. Tuberculosis in the UK. 2013 report. 2013. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317139689583
6 Podlekareva DN, Panteleev AM, Grint D, *et al*. Short and long term mortality and causes of death in HIV/TB patients in Europe. *Eur Respir J* 2014;43:166–77.
7 Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. *Int J Tuberc Lung Dis* 2011;15:871–85.
8 Abdool Karim SS, Naidoo K, Grobler A, *et al*. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010;362:697–706.
9 Blanc FX, Sok T, Laureillard D, *et al*. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011;365:1471–81.
10 Straetemans M, Bierrenbach A, Nagelkerke N, *et al*. The effect of tuberculosis on mortality in HIV positive people: a meta-analysis. *PLoS ONE* 2010;5:e15241.
11 May MT, Gompels M, Delpech V, *et al*. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy: UK cohort study. *AIDS* 2014;28:1193–202.
12 Chadborn TR, Delpech VC, Sabin CA, *et al*. The late diagnosis and consequent short-term mortality of HIV-infected heterosexuals (England and Wales, 2000–2004). *AIDS* 2006;20:2371–9.
13 Ahmed AB, Abubakar I, Delpech V, *et al*. The growing impact of HIV infection on the epidemiology of tuberculosis in England and Wales: 1999–2003. *Thorax* 2007;62:672–6.
14 Dheda K, Lampe FC, Johnson MA, *et al*. Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. *J Infect Dis* 2004;190:1670–6.
15 Dean GL, Edwards SG, Ives NJ, *et al*. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. *AIDS* 2002;16:75–83.
16 Rice B, Elford J, Yin Z, *et al*. Decreasing incidence of tuberculosis among heterosexuals living with diagnosed HIV in England and Wales. *AIDS* 2013;27:1151–7.
17 Newcombe HB. *Handbook of record linkage*. Oxford University Press, 1988.
18 Potz N, Powell D. *Manual for the probabilistic linkage of infection and death records*. Health Protection Agency, 2007.
19 Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982;69:239.
20 Akaike H. A new look at the statistical model identification. In: Parzen E, Tanabe K, Kitagawa G, eds. *Selected papers of hirotugu akaike*. New York: Springer, 1998. 215–22.
21 Simmons RD, Ciancio BC, Kall MM, *et al*. Ten-year mortality trends among persons diagnosed with HIV infection in England and Wales in the era of antiretroviral therapy: AIDS remains a silent killer. *HIV Med* 2013;14:596–604.
22 Taarnhøj G, Engsig F, Ravn P, *et al*. Incidence, risk factors and mortality of tuberculosis in Danish HIV patients 1995-2007. *BMC Pulm Med* 2011;11:1471–2466:26.
23 Michailidis C, Pozniak AL, Mandalia S, *et al*. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther (Lond)* 2005;10:417–22.
24 Harries AD, Lawn SD, Getahun H, *et al*. HIV and tuberculosis—science and implementation to turn the tide and reduce deaths. *J Int AIDS Soc* 2012;15.
25 Pozniak AL, Coyne KM, Miller RF, *et al*. British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. http://www.bhiva.org/documents/Guidelines/TB/hiv_954_online_final.pdf
26 Grant AD, Bansi L, Ainsworth J, *et al*. Tuberculosis among people with HIV infection in the United Kingdom: opportunities for prevention? *AIDS* 2009;23:2507–15.
27 Karo B, Haas W, Kollan C, *et al*. Tuberculosis among people living with HIV/AIDS in the German ClinSurv HIV Cohort: long-term incidence and risk factors. *BMC Infect Dis* 2014;14:148.
28 Delpech V, Brown AE, Croxford S, *et al*. Quality of HIV care in the United Kingdom: key indicators for the first 12 months from HIV diagnosis. *HIV Med* 2013;14(Suppl 3):19–24.
29 Wilkinson D. Drugs for preventing tuberculosis in HIV infected persons. *Cochrane Database Syst Rev* 2000;(4):CD000171 .http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed5&AN=11034676 (accessed 8 Jun 2012).
30 Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev* 2004;(1):CD000171 .http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed6&AN=14973947 (accessed 8 Jun 2012).